DATA EVALUATION RECORD

FLUTRIAFOL

OPPTS 870.4200b [§83-2b]; Carcinogenicity Study in Mice

Work Assignment No. 5-1-151 I; formerly 4-1-151 I (MRID 47090354)

Prepared for
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Template version 02/06

TXR #: 0054780

DATA EVALUATION RECORD

STUDY TYPE: Dietary carcinogenicity study in mice; OPPTS 870.4200b [§83-2b]; OECD 451.

PC CODE: 128940 **DP BARCODE**: 340368

TEST MATERIAL (PURITY): Flutriafol (93% a.i.)

SYNONYMS: α-(2-fluorophenyl)-α-(4-fluorophenyl)-1*H*-1,2,4-triazole-1-ethanol

CITATION: Hext, P.M. (1988) Flutriafol: two year feeding study in mice. Imperial Chemical Industries PLC, Cheshire, UK. Laboratory Study: PM0637, Report No. CTL/P/1930, June 3, 1988. MRID 47090354. Unpublished.

SPONSOR: Cheminova, Inc., 1600 Wilson Boulevard, Suite 700, Arlington, VA.

EXECUTIVE SUMMARY - In a carcinogenicity study (MRID 47090354), Flutriafol (93% a.i.; Batch No. P10) was administered in the diet to C57BL/10JfCD-1/Alpk mice (50/sex/dose) for up to 2 years at doses of 0 (two control groups), 10, 50, or 200 ppm (calculated to be 0, 1.1, 5.9, and 24 mg/kg bw/day in males; and 0, 1.4, 7.4 and 31 mg/kg bw/day in females).

No adverse treatment-related effects were observed on mortality or food consumption.

At 200 ppm, increased incidences were observed in discharge from the eye (both sexes) and thickened eyelids (females). Body weights were decreased ($p<=0.05$) generally throughout the study in both sexes (decr 2-8%). Overall (Weeks 1-104) body weight gains were decreased in the males (decr 18%; $p<=0.01$) and females (decr 8%; not statistically significant [NS]); and decreased ($p<=0.01$) food efficiency was observed in the males during Weeks 1-4 (decr 38%) and 1-12 (decr 21%). Additionally, increased ($p<=0.05$) platelet (incr 42%), white blood cell (incr 62%), neutrophil (incr 81%), and lymphocyte (incr 58%) counts were noted in the males. Hepatotoxicity was also noted. Increased ($p<0.01$) liver weights (absolute and adjusted for body weight) were observed in males (incr 32-37%) and females (incr 17-26%). Furthermore, increased incidences (# affected/50 in treated vs controls) of minimal to marked hepatic centrilobular fatty change were noted in the males (23 vs 1) and females (17 vs 0); and minimal to moderate hepatic centrilobular hypertrophy were noted in the males (14 vs 0-1) and females (3 vs 0).

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At 50 ppm, a slight effect was observed on body weights and body weight gains in males. Body weights were decreased by 5% ($p<=0.05$) on Week 104, and overall (Weeks 1-104) body weight gains were decreased by 8% (NS). Furthermore, a treatment-related increased incidence of hepatic centrilobular fatty change was noted in 6/50 males (1 minimal, 4 slight, and 1 marked severity). The effects of the test compound at 50 ppm were considered equivocally adverse because the effect on body weight gain was slight, only a single hepatic finding was noted, and the severity of the hepatic lesion was only minimal or slight in all but 1/50 animals.

The LOAEL is 200 ppm (24/31 mg/kg bw/day in males/females), based on hepatotoxicity (increased fatty change) in both sexes. The NOAEL is 50 ppm (5.9/7.4 mg/kg w/day).

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. There was an apparent increase in the incidence of generalized composite lymphomas in the 200 ppm female decedents (100% treated vs 62% controls). Although this finding was statistically significant ($p\leq0.05$), the difference was no longer evident when all animals were considered (92% treated vs 81-91% controls). Furthermore, the effect was not clearly dose-dependent. Dosing was considered adequate based on decreases in body weights and body weight gain in both sexes, decreased food efficiency in males, hematological findings in males, and hepatoxicity in both sexes.

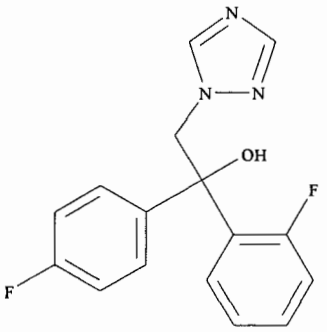
This study is classified as **acceptable/guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, Data Confidentiality, and Flagging statements were provided; however, it was stated that the Submitter neither was the Sponsor nor conductor of the study and therefore cannot be certain if the study was conducted in full accordance with 40 CFR Part 160.

I. MATERIALS AND METHODS

A MATERIALS

1. Test material: Flutriafol

Description:	Off-white powder
Batch No.:	P10
Purity:	93.0% a.i.
Stability of compound:	Stable in the diet for at least 9 weeks
CAS #:	76674-21-0
Structure:	

2. Vehicle: Diet

3. Test animals

Species:	Mouse
Strain:	C57BL/10JfCD-1/Alpk
Age and mean weight at initiation of treatment:	5-6 weeks old; 19.1-20.2 g males; 15.5-16.0 g females
Source:	Animal Breeding Unit, Imperial Chemical Industries PLC, Cheshire, UK
Housing:	Mice were housed 5/cage by sex in suspended stainless steel cages with stainless steel mesh front, back, and floors.
Diet:	CT1 diet (Special Diet Services, Ltd., Witham, Essex, UK), *ad libitum*
Water:	Filtered (0.22 µm) tap water, *ad libitum*
Environmental conditions	
Temperature:	18-29°C
Humidity:	17-74%
Air changes:	≥15/hour
Photoperiod:	12 hours light/12 hours dark
Acclimation period:	9-10 days

B. STUDY DESIGN

1. In life dates: Start: 04/01/85 End: Approximately 04/05/87

2. Animal assignment/dose levels: The animals were randomly assigned to the test groups shown in Table 1.

TABLE 1. Study design [a]		
Nominal concentration in diet (ppm)	**Dose to animal (mg/kg/day; M/F) [b]**	**104 week sacrifice; # mice/sex**
0	0	50
0	0	50
10	1.5	50
50	7.5	50
200	30	50

a Data were obtained from page 17 of MRID 47090354.

b Dose to animal estimated by the reviewer by converting the nominal dose (ppm) to mg/kg/day using the conversion factor of 1 ppm = 0.15 mg/kg/day. Thus, this is an approximate value based on nominal concentrations rather than actual compound intake, which was not reported in the study.

3. **Dose-selection rationale:** The doses used in the current study were selected based upon the results of a 29 day feeding study in mice (report number not provided). In this subchronic study, the NOAEL was 50 ppm. At 150 ppm, there were slight effects on body weight gain and liver weights, and a variety of toxicological effects were observed at 500 ppm. Finally, all mice died or were killed moribund at 1500 ppm.

4. **Dose preparation and analysis:** Dietary formulations were prepared by direct addition of the test substance to 30 kg batches of powdered diet. The frequency of diet preparation and storage temperature were not reported. Concentrations at each dietary level were measured in 16 batches (generally, every 1-2 months). Prior to dosing, homogeneity (top, middle, bottom) was evaluated in this study at 10 ppm and in previous studies (report numbers not provided) at 20, 100, 2000, and 5000. Prior to dosing, the stability of the test compound was demonstrated in 60 and 1000 ppm dietary formulations for 27 days and 50 and 1500 ppm dietary formulations for 68 days in previous studies (report numbers not provided). The temperature during stability testing was not reported and is assumed to be room temperature.

Results

Homogeneity (% coefficient of variation): 1.0-2.2%, except 8.3% at 20 ppm

Stability (% of initial concentration): 95-100%

Concentration analysis (% of nominal concentration):

Dose	Conc. Range (% nominal)
10 ppm	85-108
50 ppm	85-104
200 ppm	90-100

All but 5 diets analyzed had concentrations that were within 10% of nominal levels. The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Statistical differences between control and treated groups were expressed at the 1% or 5% level. All data were checked (method not reported) for unusual values and where such values were detected the analyses were repeated omitting these values to determine their influence on the conclusions.

PARAMETER	ANALYSIS CONDUCTED
Body weight gain Body weight Food consumption Food utilization Hematological parameters	Analysis of variance (ANOVA) was used to determine differences among groups. 2-sided Student's t-test, using unbiased estimates of treatment group means by the least square means method, was performed for pair-wise comparisons of treated groups with the pooled control groups
Liver weights	Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) on terminal bodyweight were used to determine differences among groups. 2-sided Student's t-test, using unbiased estimates of treatment group means by the least square means method, was performed for pair-wise comparisons of treated groups with the pooled control groups
Survival	Kaplan-Meier survival estimate of the survival function was performed. The logrank test was used to compare the survival distributions of each treatment group with the pooled control group
Neoplastic and non-neoplastic pathology	One-sided Fisher's Exact Test was used for pair-wise comparisons of treated groups with the pooled control groups. Peto's test for positive trend was performed.

These statistical analyses were considered appropriate.

C. METHODS

1. Observations

1a. Cageside observations: All animals were inspected at least once daily for evidence of morbidity or mortality.

1b. Clinical examinations: Detailed clinical examinations were conducted weekly on all animals.

1c. Neurological evaluations: Although neurological evaluations were not performed in this study; acute (MRID 47090408) and subchronic (MRID 47090410) neurotoxicity studies were performed in rats, and these reports were submitted concurrently.

2. **Body weight and body weight gain:** The weight of each mouse was recorded on the day that treatment commenced, at weekly intervals for the first 12 weeks of treatment, thereafter once every 2 weeks, and at termination. Cumulative body weight gains were reported each time the mice were weighed.

3. **Food consumption. food utilization, and compound intake:** Food consumption (g/mouse/day) was recorded for each cage of mice each week for the first twelve weeks and every fourth week thereafter. Food utilization per cage was calculated weekly for the first twelve weeks from the weight gained by the animals per 100 g of food consumed. Compound intake (mg/kg bw/day) values were not reported.

4 **Ophthalmoscopic examination:** Ocular examinations were not performed and are not required by the guideline (OPPTS 870.4200b).

5. **Hematology and clinical chemistry:** At 12 and 18 months, blood smears were prepared from a minimum of 10 mice/sex/group using blood from the tail vein. Leukocyte differential counts were performed, and morphological appearance of red blood cells was evaluated. Blood samples were collected by cardiac puncture from all mice surviving to study termination, and the following parameters were measured:

X	Hematocrit (HCT)	X	Leukocyte differential count*
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)	X	Mean corpuscular volume (MCV)
X	Platelet count*		Reticulocyte count
	Blood clotting measurements	X	Red blood cell morphology
	(Activated partial thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Minimum required for carcinogenicity studies (Cont. and HDT unless effects are observed) based on Guideline 870.4200 and OECD 451

Clinical chemistry analyses were not performed and are not required by the guideline (OPPTS 870.4200b).

6. **Urinalysis:** Urinalysis was not performed and is not required by the guideline (OPPTS 870.4200b).

7. **Sacrifice and pathology:** All surviving mice were killed by over-exposure to halothane BP vapor followed by exsanguination during Weeks 105 and 106. All mice, including decedents when possible, were subjected to a full necropsy. The CHECKED (X) tissues were collected for histological examination. The liver was also weighed (XX).

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta *	X	Brain (multiple sections)*+
X	Salivary glands*	X	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	X	Thymus		GLANDULAR
X	Ileum*			X	Adrenal gland*+
X	Cecum*		UROGENITAL		Lacrimal gland
X	Colon*	X	Kidneys*+		Parathyroids*
X	Rectum*	X	Urinary bladder*	X	Thyroids*
XX	Liver*+	X	Testes*+		OTHER
X	Gall bladder*	X	Epididymides*+	X	Bone (femur)
	Bile duct	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicle*	X	Skin*
	RESPIRATORY	X	Ovaries*+	X	Harderian gland
X	Trachea*	X	Uterus*+	X	All gross lesions and masses*
X	Lung*++	X	Mammary gland* (female only)		
X	Nose*		Vagina		
	Pharynx*	X	Cervix		
	Larynx*	X	Preputial gland (males only)		

* Required for carcinogenicity studies based on Guideline 870.4200.
\+ Organ weight required in carcinogenicity studies.
++ Organ weight required if inhalation route.

Eyes and Harderian glands were fixed in Davidson's fixative. Skin, testis, and epididymis were fixed in Bouin's fixative. All other tissues were fixed in 10% neutral buffered formol saline. The nasal cavity was perfused and stored. All other samples were routinely processed and stained with hematoxylin and eosin. Pathological findings were graded as minimal, slight, moderate, or marked.

8. **Microbiological sentinels:** Additional animals were used to verify that infection did not compromise this study. Extra animals (5/sex/dose) were treated with 200 ppm Flutriafol or control diets for 104 weeks and were checked daily for any change in clinical condition. Moribund animals were killed and examined by a microbiologist. The results indicated no evidence of disease or infection which would have compromised the study.

II. RESULTS

A. OBSERVATIONS

1. **Mortality:** No treatment-related effect was observed on mortality. Survival exceeded guideline requirements of 50% at 15 months and 25% at 18 months in both sexes.

2. **Clinical signs of toxicity:** Increased incidences of the following clinical signs were observed at 200 ppm:
(i) discharge from eye (172 observations in 21 males beginning at Week 20 in the treated group vs 60 observations in 9 males beginning at Week 43 in the control group);
(ii) eyelids thickened in males (205 observations in 20 males beginning at Week 40 in the treated group vs 72 observations in 6 males beginning at Week 36 in the control group); and
(iii) discharge from eye (240 observations in 18 females beginning at Week 17 in the treated group vs 63 observations in 9 females beginning at Week 74 in the control group).

B. BODY WEIGHT: Selected body weights and body weight gains are presented in Table 2. Body weights were decreased ($p \leq 0.05$) generally throughout the study in the 200 ppm males (↓3-8%) and females (↓2-5%). Body weights were also decreased ($p \leq 0.05$) in the 50 ppm males on Week 104 (↓5%) and females on Weeks 5-13, 31, and 59 (↓2-5%). Overall (Weeks 1-104) body weight gains were decreased in the males at 50 ppm (↓8%; not statistically significant [NS]) and 200 ppm (↓18%; $p \leq 0.01$) and in the 200 ppm females (↓8%; NS). The effect on the 50 ppm females on body weights was minor and transient and overall body weight gain exceeded controls. Other differences ($p < 0.05$) in body weights and body weight gain were transient and minor. The decreases in body weight were less than 10% and are not considered to be adverse.

TABLE 2. Mean body weights and body weight gains (g) at selected intervals in mice treated with flutriafol in the diet for up to 2 years. [a]

Week	Dose (ppm)			
	0 [b]	10	50	200
Males (n=25-50)				
1	19.4	20.2	19.7	20.1
2	21.3	21.7	21.6	20.6* (↓3)
13	28.8	28.6	28.9	27.4** (↓5)
51	34.2	34.2	33.7	32.3** (↓5)
83	34.8	34.2	34.4	32.0** (↓8)
104	33.6	33.2	32.2* (↓5)	31.5** (↓6)
BWG (1-13) [c]	9.5	8.4	9.2 (↓3)	7.3 (↓23)
BWG (13-51) [c]	5.3	5.1	4.8 (↓9)	4.9 (↓8)
BWG (51-104) [c]	-0.6	-0.6	-1.5 (↓173)	-0.8 (↓45)
BWG (1-104)	13.7	12.8	12.6 (↓8)	11.2** (↓18)
Females (n=22-50)				
0	16.0	15.5	15.9	15.7
5	20.8	20.6	19.8** (↓5)	19.7** (↓5)
6	21.4	21.3	20.9** (↓2)	20.5** (↓4)
7	21.7	21.6	21.3* (↓2)	21.2** (↓2)
13	23.6	23.7	23.2* (↓2)	22.9** (↓3)
29	25.7	25.7	25.2	24.5** (↓5)
51	26.8	27.0	26.4	25.8** (↓4)
104	27.9	27.8	28.0	26.4* (↓5)
BWG (1-13) [c]	7.7	8.2	7.3	7.2 (↓6)
BWG (13-51) [c]	3.2	3.3	3.2	2.9 (↓9)
BWG (51-104) [c]	1.0	0.8	1.6	0.6 (↓43)
BWG (1-104)	11.8	12.2	12.0	10.9 (↓8)

a Data were obtained from Table 6-7 on pages 70-85 of MRID 47090354. Standard deviations were not reported. Percent difference from controls, calculated by reviewers, is included in parentheses.

b A mean of the means for each control group (calculated by the reviewers) is reported as an approximation of the value for the pooled controls (to which the treatment groups were compared statistically by the Sponsor). Survival was generally similar between the two control groups, allowing the mean to serve as an approximation for the pooled controls.

c Body weight gain (BWG) was calculated by the reviewers from data presented in this table.

* Significantly different ($p \leq 0.05$) from the pooled control groups

** Significantly different ($p \leq 0.01$) from the pooled control groups

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. **Food consumption:** No adverse treatment-related effect was observed on food consumption. Decreased ($p \leq 0.05$) food consumption was noted in the 200 ppm males on Weeks 2, 11, 28, 32, 36, and 48, and 1-12 (↓3-8%) and females on Weeks 6 and 48 (↓5-7%). These differences were minor and transient. Other differences ($p \leq 0.05$) were observed in the 10 and 50 ppm treatment groups that were minor, transient, and unrelated to dose.

2. **Compound consumption:** Compound intake was not reported.

3. **Food utilization:** Decreased ($p \leq 0.01$) food utilization was observed in the 200 ppm males during Weeks 1-4 (↓38%) and 1-12 (↓21%). Differences ($p \leq 0.05$) in other treatment groups were unrelated to dose.

D. HEMATOLOGY: Increased ($p \leq 0.05$) platelet (↑42%), white blood cell (↑62%), neutrophil (↑81%), and lymphocyte (↑58%) counts were noted in the 200 ppm males (Table 3). All other differences ($p < 0.05$) from the controls were minor and/or unrelated to dose.

TABLE 3. Selected hematological parameters in male mice treated with flutriafol in the diet for up to 2 years. [a]

Parameter	Dose (ppm)			
	0 [b]	10	50	200
Platelet count ($x10^9$/L)	2084	2495	2317	2952** (↑42)
White blood cell count ($x10^9$/L)	7.67	7.65	11.16	12.45* (↑62)
Neutrophil count ($x10^9$/L)	1.79	1.79	2.91	3.24* (↑81)
Lymphocyte count ($x10^9$/L)	5.52	5.50	7.85	8.71* (↑58)

a Data (n=24-29, except 52 for pooled controls) were obtained from Table 10 on pages 95-96 of MRID 47090354. Standard deviations were not reported. Percent difference from controls, calculated by reviewers, is included in parentheses.
b Means for pooled control groups were calculated by the reviewers.
* Significantly different ($p \leq 0.05$) from the pooled control groups
** Significantly different ($p \leq 0.01$) from the pooled control groups

E. SACRIFICE AND PATHOLOGY

1. **Organ weights:** Increased ($p \leq 0.01$) liver weights (absolute and adjusted for body weight) were observed at 200 ppm in males (↑32-37%) and females (↑17-26%; Table 4).

TABLE 4. Liver weights in mice treated with flutriafol in the diet for up to 2 years. [a]

Liver weight	Dose (ppm)			
	0 [b]	10	50	200
Males				
Organ Weight	1.66	1.63	1.68	2.19** (↑32)
Adjusted for body weight [c]	1.64	1.61	1.70	2.24** (↑37)
Females				
Organ Weight	1.52	1.55	1.46	1.78** (↑17)
Adjusted for body weight	1.49	1.55	1.44	1.87** (↑26)

a Data (n=23-31, except 51-53 for pooled controls) were obtained from Table 11 on page 97 of MRID 47090354. Standard deviations were not reported. Percent difference from controls, calculated by reviewers, is included in parentheses.
b Means for pooled control groups were calculated by the reviewers.
c Adjusted for body weight through analysis of covariance on terminal bodyweight
** Significantly different ($p \leq 0.01$) from the pooled control groups

2. **Gross pathology:** An increased incidence of single masses was noted in the jejunum of the 200 ppm females (8/50 treated mice vs 2-3/50 controls); however, histological evaluation did not support an increase in neoplasia, and no further evidence of toxicity to the jejunum was noted. Therefore, this finding was considered incidental.

3. Microscopic pathology

a. Non-neoplastic: Increased incidences (# affected/50 in treated vs controls) of the following findings were observed: minimal to marked hepatic centrilobular fatty change in males at 50 (6 vs 1) and 200 (23) ppm and in 200 ppm females (17 vs 0); and minimal to moderate hepatic centrilobular hypertrophy in 200 ppm males (14 vs 0-1) and females (3 vs 0; Table 5). The incidences of all other findings in the treatment groups were similar to the control groups.

TABLE 5. Incidence of selected microscopic findings in mice treated with flutriafol in the diet for up to 2 years. [a]

Lesion		Dose (ppm)				
		0	0 [b]	10	50	200
Males						
Liver	Centrilobular fatty change (total)	1	1	2	6	23
	Minimal	1	0	1	1	1
	Slight	0	1	0	4	10
	Moderate	0	0	1	0	8
	Marked	0	0	0	1	4
	Centrilobular hypertrophy (total)	1	0	1	1	14
	Minimal	1	0	0	1	3
	Slight	0	0	0	0	7
	Moderate	0	0	1	0	4
Females						
Liver	Centrilobular fatty change (total)	0	0	1	2	17
	Minimal	0	0	0	2	2
	Slight	0	0	1	0	4
	Moderate	0	0	0	0	7
	Marked	0	0	0	0	4
	Centrilobular hypertrophy (total)	0	0	0	1	3
	Slight	0	0	0	0	1
	Moderate	0	0	0	1	2

a Data (n=50) were obtained from Table 14 on pages 175 and 199 of MRID 47090354.
b This study ran 2 control groups in parallel.

b. Neoplastic: The incidences of neoplastic lesions are reported in Tables 17-18 on pages 281-304 in MRID 47090354 and are included as an attachment to this DER. No treatment-related effect on neoplasia was observed. There was an apparent increase in the incidence of generalized composite lymphomas in the 200 ppm female decedents (100% treated vs 62% controls; Table 6). Although this finding was statistically significant ($p \leq 0.05$), the difference was no longer evident when all animals were considered (92% treated vs 81-91% controls). Furthermore, the effect was not clearly dose-dependent. This finding was extremely common even in the controls, and was not considered treatment-related.

TABLE 6. Incidence [#affected/# observed (%)] of generalized composite lymphoma in female mice treated with flutriafol in the diet for up to 2 years. [a]

Group	Dose (ppm)				
	0	0 [b]	10	50	200
Decedents	5/8 (62)	10/16 (62)	11/13 (85)	6/10 (60)	15/15* (100)
All animals combined	29/32 (91)	25/31 (81)	25/27 (93)	14/19 (74)	33/36 (92)

a Data (n=50) were obtained from Table 17 (page 286) and Table 18 (page 295) of MRID 47090354.
b This study ran 2 control groups in parallel.
* Significantly different ($p \leq 0.05$) from the pooled control groups

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATOR'S CONCLUSIONS: At 200 ppm, the following observations were noted: decreased body weight gain in both sexes; increased platelet, white blood cell, neutrophil, and lymphocyte counts in males; increased liver weights in both sexes, and increased incidence of fatty change in the liver and hepatic centrilobular hypertrophy in both sexes. Some evidence for similar but less severe effects on the liver were noted at 50 ppm, and the NOAEL was 10 ppm. There was no evidence of treatment-related neoplasia.

B. REVIEWER COMMENTS: No adverse treatment-related effects were observed on mortality or food consumption.

Increased incidences were observed in the following clinical signs at 200 ppm:
(i) discharge from eye (172 observations in 21 males beginning at Week 20 in the treated group vs 60 observations in 9 males beginning at Week 42 in the control group);
(ii) eyelids thickened (205 observations in 20 males beginning at Week 40 in the treated group vs 72 observations in 6 males beginning at Week 36 in the control group); and
(iii) discharge from eye (240 observations in 18 females beginning at Week 17 in the treated group vs 63 observations in 9 females beginning at Week 74 in the control group).

Body weights were decreased ($p \leq 0.05$) generally throughout the study in the 200 ppm males (↓3-8%) and females (↓2-5%). Body weights were also decreased ($p \leq 0.05$) in the 50 ppm males on Week 104 (↓5%) and females on Weeks 5-13, 31, and 59 (↓2-5%). Overall (Weeks 1-104) body weight gains were decreased in the males at 50 ppm (↓8%; not statistically significant [NS]) and 200 ppm (↓18%; $p \leq 0.01$) and in the 200 ppm females (↓8%; NS).

Only, a slight effect on body weight and body weight gain was observed in the 50 ppm males. A statistically significant decrease was only observed in the terminal body weight, and the overall body weight gain was not statistically different. However, a 8% decrease in overall bodyweight gain was noted, and the effect on the terminal body weight and overall body weight gain was dose-dependent.

Other effects observed in the 200 ppm males included: decreased ($p \leq 0.01$) food efficiency during Weeks 1-4 (↓38%) and 1-12 (↓21%); and increased ($p \leq 0.05$) platelet (↑42%), white blood cell (↑62%), neutrophil (↑81%), and lymphocyte (↑58%) counts.

Increased ($p \leq 0.01$) liver weights (absolute and adjusted for body weight) were observed at 200 ppm in males (↑32-37%) and females (↑17-26%). Increased incidences (# affected/50 in treated vs controls) of the following findings were observed: minimal to marked hepatic centrilobular fatty change in males at 50 (6 vs 1) and 200 (23) ppm and in 200 ppm females (17 vs 0); and minimal to moderate hepatic centrilobular hypertrophy in 200 ppm males (14 vs 0-1) and females (3 vs 0).

At 50 ppm, a slight effect was observed on body weights and body weight gains in males. Body weights were decreased by 5% ($p <= 0.05$) on Week 104, and overall (Weeks 1-104) body weight gains were decreased by 8% (NS). Furthermore, a treatment-related increased incidence of hepatic centrilobular fatty change was noted in 6/50 males (1 minimal, 4 slight, and 1 marked severity).

The LOAEL is 200 ppm (24/31 mg/kg bw/day in males/females), based on hepatotoxicity (increased fatty change) in both sexes. The NOAEL is 50 ppm (5.9/7.4 mg/kg w/day).

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. There was an apparent increase in the incidence of generalized composite lymphomas in the 200 ppm female decedents (100% treated vs 62% controls). Although this finding was statistically significant ($p \leq 0.05$), the difference was no longer evident when all animals were considered (92% treated vs 81-91% controls). Furthermore, the effect was not clearly dose-dependent. Dosing was considered adequate based on decreases in body weights and body weight gain in both sexes, decreased food efficiency in males, hematological findings in males, and hepatoxicity in both sexes.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

C. **STUDY DEFICIENCIES:** The following study deficiencies were noted but do not alter the conclusions of this DER:

- $ No nose, pharynx, larynx, or parathyroid histological evaluations were performed.
- $ Actual compound intake was not reported.
- $ No historical data were reported for neoplasia.
- $ Frequency of diet preparation and storage temperature were not reported.

$ Only the liver was weighed.

ATTACHMENT

The following pages are excerpts from Tables 17-18 on pages 281-304 in MRID 47090354.

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

NEOPLASTIC MORPHOLOGIES	Dietary concentration of Flutriafol				
SEX: MALES	0 ppm	3 ppm	10 ppm	50 ppm	200 ppm
MALES ON STUDY	50	50	50	50	50
ANIMALS COMPLETED	50	50	50	50	50
ADRENAL GLAND					
EXAMINED	49	48	50	49	48
MISSING	1	2	0	1	2
Cortical adenoma..(BENIGN)	2	0	0	0	0
BLADDER					
EXAMINED	48	48	50	50	49
MISSING	2	2	0	0	1
Histiocytic sarcoma..(MALIGNANT)	0	1	0	0	0
BONE MARROW					
EXAMINED	49	50	48	48	49
MISSING	1	0	2	2	1
Histiocytic sarcoma..(MALIGNANT)	0	0	1	0	0
EPIDIDYMIS					
EXAMINED	50	50	50	49	50
MISSING	0	0	0	1	0
Histiocytic sarcoma..(MALIGNANT)	2	2	0	0	0
FOOT/LEG					
EXAMINED	2	2	2	2	6
Fibrosarcoma..(MALIGNANT)	0	0	0	0	1
GENERALISED NEOPLASIA					
EXAMINED	29	19	23	30	26
Composite lymphoma..(MALIGNANT)	27	17	21	26	24
Lymphoblastic/lymphocytic lymphoma..(MALIGNANT)	0	1	0	0	0
Histiocytic sarcoma..(MALIGNANT)	2	1	2	4	2
Lymphoma..(MALIGNANT)	0	0	1	0	0
HARDERIAN GLAND					
EXAMINED	48	47	48	50	50
MISSING	2	3	2	0	0

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

NEOPLASTIC MORPHOLOGIES	Dietary concentration of Flutriafol				
SEX: MALES	0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
MALES ON STUDY	50	50	50	50	50
ANIMALS COMPLETED	50	50	50	50	50
HARDERIAN GLAND (CONTINUED)					
Adenoma..(BENIGN)	0	0	0	1	0
Cystadenoma..(BENIGN)	0	1	0	0	0
LIVER					
EXAMINED	50	50	50	50	50
Hepatocellular adenoma..(BENIGN)	1	0	1	1	2
Hepatocellular carcinoma..(MALIGNANT)	0	0	0	1	0
Angiosarcoma..(MALIGNANT)	2	4	3	3	4
Histiocytic sarcoma..(MALIGNANT)	3	4	0	2	3
LUNG					
EXAMINED	50	50	50	49	49
MISSING	0	0	0	1	1
Adenoma..(BENIGN)	2	2	3	2	2
Adenocarcinoma..(MALIGNANT)	0	1	0	1	0
LYMPH NODE-CERVICAL					
EXAMINED	43	48	49	49	49
MISSING	7	2	1	1	1
Composite lymphoma..(MALIGNANT)	0	1	0	0	0
LYMPH NODE-INGUINAL					
EXAMINED	1	0	0	3	0
Angiosarcoma..(MALIGNANT)	0	0	0	1	0
LYMPH NODE-MESENTERIC					
EXAMINED	48	46	50	50	48
MISSING	2	4	0	0	2
Composite lymphoma..(MALIGNANT)	1	1	2	1	0
Histiocytic sarcoma..(MALIGNANT)	0	1	1	1	1
Lymphoblastic/lymphocytic lymphoma..(MALIGNANT)	1	1	0	0	0
LYMPH NODE-THYMIC					
EXAMINED	13	12	14	18	12

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

NEOPLASTIC MORPHOLOGIES	Dietary concentration of flutriafol				
SEX: MALES	0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
MALES ON STUDY	50	50	50	50	50
ANIMALS COMPLETED	50	50	50	50	50
LYMPH NODE-THYMIC (CONTINUED)					
Composite lymphoma..(MALIGNANT)	0	0	0	1	0
Histiocytic sarcoma..(MALIGNANT)	0	1	0	0	0
PITUITARY GLAND					
EXAMINED	40	41	44	44	43
MISSING	10	7	6	6	7
Adenoma..(BENIGN)	1	0	0	2	0
PREPUTIAL GLAND					
EXAMINED	48	43	48	49	48
MISSING	2	7	2	1	2
Histiocytic sarcoma..(MALIGNANT)	1	0	1	0	1
SKIN					
EXAMINED	50	50	50	50	50
Rhabdomyosarcoma..(MALIGNANT)	1	0	0	0	0
SPINAL CORD					
EXAMINED	50	49	50	49	50
MISSING	0	1	0	1	0
Malignant meningioma..(MALIGNANT)	0	1	0	0	0
SPLEEN					
EXAMINED	50	48	50	50	50
MISSING	0	2	0	0	0
Composite lymphoma..(MALIGNANT)	0	0	1	0	0
Angiosarcoma..(MALIGNANT)	1	0	1	0	1
Histiocytic sarcoma..(MALIGNANT)	2	0	1	0	1
STOMACH					
EXAMINED	48	46	48	49	47
MISSING	2	4	2	1	3

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

NEOPLASTIC MORPHOLOGIES	SEX: MALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	MALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	50	50	50	50	50
STOMACH (CONTINUED)						
Squamous papilloma..(BENIGN)		0	0	0	2	0
Papilloma..(BENIGN)		0	0	0	1	0
SUBCUTANEOUS TISSUE						
EXAMINED		4	3	2	1	1
Fibroma..(BENIGN)		0	0	1	0	0
Neurofibrosarcoma..(MALIGNANT)		1	0	0	0	0
TESTIS						
EXAMINED		50	50	50	48	48
MISSING		0	0	0	2	2
Benign Leydig cell tumour..(BENIGN)		1	0	0	1	0
Malignant Leydig cell tumour..(MALIGNANT)		1	0	0	0	0
Histiocytic sarcoma..(MALIGNANT)		2	1	1	1	1
THYMUS						
EXAMINED		38	41	42	41	39
MISSING		12	9	8	9	11
Composite lymphoma..(MALIGNANT)		2	0	1	1	1
THYROID GLAND						
EXAMINED		42	47	48	49	47
MISSING		8	3	2	1	3
Adenoma..(BENIGN)		0	1	1	0	2
VOLUNTARY MUSCLE						
EXAMINED		50	50	50	50	48
MISSING		0	0	0	0	2
Rhabdomyosarcoma..(MALIGNANT)		0	0	0	0	1
ZYMBALS GLAND/EAR						
EXAMINED		0	1	0	0	0

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

NEOPLASTIC MORPHOLOGIES	SEX: MALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	50	50	50	50	50
ZYMBALS GLAND/EAR (CONTINUED)						
Squamous cell carcinoma..(MALIGNANT)		0	1	0	0	0

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

NEOPLASTIC MORPHOLOGIES	Dietary concentration of Flutriafol				
SEX: FEMALES	0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
FEMALES ON STUDY	50	50	50	50	50
ANIMALS COMPLETED	50	50	50	50	50
ADRENAL GLAND					
EXAMINED	49	48	49	49	50
MISSING	1	2	1	1	0
Cortical adenoma..(BENIGN)	1	0	0	0	0
BLADDER					
EXAMINED	50	49	48	46	49
MISSING	0	1	2	4	1
Histiocytic sarcoma..(MALIGNANT)	1	0	0	0	0
BONE MARROW					
EXAMINED	49	50	50	50	50
MISSING	1	0	0	0	0
Histiocytic sarcoma..(MALIGNANT)	0	0	0	1	0
Angioma..(BENIGN)	0	0	1	0	0
BONE(FEMUR)					
EXAMINED	49	50	50	50	50
MISSING	1	0	0	0	0
Osteosarcoma..(MALIGNANT)	0	0	1	0	0
CERVIX					
EXAMINED	46	46	49	47	46
MISSING	4	4	1	3	4
Histiocytic sarcoma..(MALIGNANT)	3	2	2	3	2
GENERALISED NEOPLASIA					
EXAMINED	32	31	27	19	36
Composite lymphoma..(MALIGNANT)	29 91	25 81	25 93	14 74	33 92
Lymphoblastic/lymphocytic lymphoma..(MALIGNANT)	0	0	1	2	0
Histiocytic sarcoma..(MALIGNANT)	2	5	2	3	4
Myeloid leukaemia..(MALIGNANT)	1	1	0	0	0

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

NEOPLASTIC MORPHOLOGIES	Dietary concentration of Flutriafol				
SEX: FEMALES	0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
FEMALES ON STUDY	50	50	50	50	50
ANIMALS COMPLETED	50	50	50	50	50
GENERALISED NEOPLASIA (CONTINUED)					
Lymphoma..(MALIGNANT)	1	0	0	0	0
HARDERIAN GLAND					
EXAMINED	47	49	49	49	50
MISSING	3	1	1	1	0
Adenoma..(BENIGN)	1	0	1	0	0
JEJUNUM					
EXAMINED	49	46	48	48	49
MISSING	1	4	2	2	1
Histiocytic sarcoma..(MALIGNANT)	0	0	0	0	1
KIDNEY					
EXAMINED	50	50	50	50	50
Sarcoma..(MALIGNANT)	0	0	1	0	0
LIVER					
EXAMINED	50	50	50	50	50
Hepatocellular adenoma..(BENIGN)	0	1	0	0	0
Angiosarcoma..(MALIGNANT)	3	1	0	2	1
Histiocytic sarcoma..(MALIGNANT)	4	3	2	4	6
Composite lymphoma..(MALIGNANT)	1	0	1	0	0
LUNG					
EXAMINED	50	50	50	50	50
Adenoma..(BENIGN)	1	2	1	1	1
Adenocarcinoma..(MALIGNANT)	1	0	1	0	0
LYMPH NODE-HEPATIC					
EXAMINED	10	7	7	10	9
Composite lymphoma..(MALIGNANT)	0	1	0	2	0

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TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

NEOPLASTIC MORPHOLOGIES	Dietary concentration of Flutriafol				
SEX: FEMALES	0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
FEMALES ON STUDY	50	50	50	50	50
ANIMALS COMPLETED	50	50	50	50	50
LYMPH NODE-HEPATIC (CONTINUED)					
Histiocytic sarcoma..(MALIGNANT)	0	0	0	1	0
LYMPH NODE-MESENTERIC					
EXAMINED	50	50	49	48	50
MISSING	0	0	1	2	0
Composite lymphoma..(MALIGNANT)	2	1	2	0	0
Histiocytic sarcoma..(MALIGNANT)	0	1	1	1	0
Lymphoblastic/lymphocytic lymphoma..(MALIGNANT)	0	1	0	0	0
LYMPH NODE-THYMIC					
EXAMINED	13	21	14	14	18
MISSING	0	1	0	0	0
Histiocytic sarcoma..(MALIGNANT)	0	1	0	0	0
OVARY					
EXAMINED	49	50	49	49	46
MISSING	1	0	1	1	4
Adenoma..(BENIGN)	0	0	1	1	0
Granulosa cell tumour..(BENIGN)	0	0	0	1	0
Histiocytic sarcoma..(MALIGNANT)	0	0	0	1	0
Haemangioma..(BENIGN)	0	1	0	0	0
PITUITARY GLAND					
EXAMINED	46	46	41	45	42
MISSING	4	4	9	5	8
Adenoma..(BENIGN)	9	11	11	10	6
Carcinoma..(MALIGNANT)	0	0	0	0	1
SKIN					
EXAMINED	50	50	50	50	50
Fibroma..(BENIGN)	0	1	0	0	0
SKULL					
EXAMINED	0	0	0	0	1

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FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

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NEOPLASTIC MORPHOLOGIES	SEX: FEMALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	50	50	50	50	50
SKULL (CONTINUED)						
Osteosarcoma..(MALIGNANT)		0	0	0	0	1
SPLEEN						
EXAMINED		50	50	50	50	50
Composite lymphoma..(MALIGNANT)		0	0	1	0	0
Angiosarcoma..(MALIGNANT)		0	0	1	0	0
Histiocytic sarcoma..(MALIGNANT)		0	0	0	0	1
SUBCUTANEOUS TISSUE						
EXAMINED		3	6	3	0	3
Fibrosarcoma..(MALIGNANT)		0	0	1	0	0
Histiocytic sarcoma..(MALIGNANT)		0	1	1	0	0
THYMUS						
EXAMINED		46	44	47	46	42
MISSING		4	6	3	4	8
Histiocytic sarcoma..(MALIGNANT)		0	1	0	0	0
THYROID GLAND						
EXAMINED		49	45	49	46	47
MISSING		1	5	1	4	3
Adenoma..(BENIGN)		1	0	1	0	0
Parafollicular cell tumour..(BENIGN)		0	1	0	0	0
UTERUS						
EXAMINED		50	49	49	50	50
MISSING		0	1	1	0	0
Adenoma..(BENIGN)		1	0	0	2	0
Adenocarcinoma..(MALIGNANT)		1	0	0	0	1
Histiocytic sarcoma..(MALIGNANT)		1	3	3	4	2
Leiomyoma..(BENIGN)		0	0	0	1	1

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 17
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (ALL ANIMALS)

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NEOPLASTIC MORPHOLOGIES	SEX: FEMALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	50	50	50	50	50
UTERUS (CONTINUED)						
Angioma..(BENIGN)		0	0	1	0	0
Composite lymphoma..(MALIGNANT)		0	0	0	1	0

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 18
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)

NEOPLASTIC MORPHOLOGIES REMOVAL REASON: INTERCURRENT	SEX: MALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	MALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	25	22	22	19	25
ADRENAL GLAND						
EXAMINED		25	20	22	19	25
MISSING		0	2	0	0	0
Cortical adenoma..(BENIGN)		1	0	0	0	0
BONE MARROW						
EXAMINED		25	22	22	19	25
Histiocytic sarcoma..(MALIGNANT)		0	0	1	0	0
EPIDIDYMIS						
EXAMINED		25	22	22	18	25
MISSING		0	0	0	1	0
Histiocytic sarcoma..(MALIGNANT)		0	1	0	0	0
FOOT/LEG						
EXAMINED		2	1	1	2	6
Fibrosarcoma..(MALIGNANT)		0	0	0	0	1
GENERALISED NEOPLASIA						
EXAMINED		10	5	10	11	10
Composite Lymphoma..(MALIGNANT)		8	3	8	7	8
Lymphoblastic/lymphocytic lymphoma..(MALIGNANT)		0	1	0	0	0
Histiocytic sarcoma..(MALIGNANT)		2	1	2	4	2
Lymphoma..(MALIGNANT)		0	0	1	0	0
HARDERIAN GLAND						
EXAMINED		23	20	20	19	25
MISSING		2	2	2	0	0
Adenoma..(BENIGN)		0	0	0	1	0
LIVER						
EXAMINED		25	22	22	19	25

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 18
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)

NEOPLASTIC MORPHOLOGIES REMOVAL REASON: INTERCURRENT	SEX: MALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	MALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	25	22	22	19	25
LIVER (CONTINUED)						
Angiosarcoma..(MALIGNANT)		1	2	1	0	3
Histiocytic sarcoma..(MALIGNANT)		3	4	0	2	2
LUNG						
EXAMINED		25	22	22	18	24
MISSING		0	0	0	1	1
Adenoma..(BENIGN)		1	2	0	1	0
LYMPH NODE-CERVICAL						
EXAMINED		20	21	21	19	24
MISSING		5	1	1	0	1
Composite lymphoma..(MALIGNANT)		0	1	0	0	0
LYMPH NODE-MESENTERIC						
EXAMINED		23	18	22	19	23
MISSING		2	4	0	0	2
Composite lymphoma..(MALIGNANT)		0	1	1	0	0
Histiocytic sarcoma..(MALIGNANT)		0	1	1	1	1
Lymphoblastic/lymphocytic lymphoma..(MALIGNANT)		1	1	0	0	0
PITUITARY GLAND						
EXAMINED		17	19	19	14	22
MISSING		8	3	3	5	3
Adenoma..(BENIGN)		0	0	0	1	0
PREPUTIAL GLAND						
EXAMINED		24	17	20	18	24
MISSING		1	5	2	1	1
Histiocytic sarcoma..(MALIGNANT)		0	0	0	0	1
SPINAL CORD						
EXAMINED		25	21	22	19	25
MISSING		0	1	0	0	0

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 18
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)
PAGE: 3

NEOPLASTIC MORPHOLOGIES REMOVAL REASON: INTERCURRENT	SEX: MALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	MALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	25	22	22	19	25
SPINAL CORD	(CONTINUED)					
Malignant meningioma..(MALIGNANT)		0	1	0	0	0
SPLEEN						
EXAMINED		25	20	22	19	25
MISSING		0	2	0	0	0
Composite lymphoma..(MALIGNANT)		0	0	1	0	0
Angiosarcoma..(MALIGNANT)		1	0	0	0	1
Histiocytic sarcoma..(MALIGNANT)		2	0	1	0	1
TESTIS						
EXAMINED		25	22	22	17	23
MISSING		0	0	0	2	2
Benign Leydig cell tumour..(BENIGN)		1	0	0	1	0
Malignant Leydig cell tumour..(MALIGNANT)		1	0	0	0	0
Histiocytic sarcoma..(MALIGNANT)		1	0	0	0	0
THYMUS						
EXAMINED		18	15	17	18	18
MISSING		7	7	5	1	7
Composite lymphoma..(MALIGNANT)		2	0	0	0	1
THYROID GLAND						
EXAMINED		19	19	21	18	24
MISSING		6	3	1	1	1
Adenoma..(BENIGN)		0	0	0	0	1
VOLUNTARY MUSCLE						
EXAMINED		25	22	22	19	24
MISSING		0	0	0	0	1
Rhabdomyosarcoma..(MALIGNANT)		0	0	0	0	1
ZYMBALS GLAND/EAR						
EXAMINED		0	1	0	0	0

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 18
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)
PAGE: 4

NEOPLASTIC MORPHOLOGIES REMOVAL REASON: INTERCURRENT	SEX: MALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	25	22	22	19	25
ZYMBALS GLAND/EAR	(CONTINUED)					
Squamous cell carcinoma..(MALIGNANT)		0	1	0	0	0

FLUTRIAFOL : TWO YEAR FEEDING STUDY IN MICE
TABLE 18
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)
PAGE: 5

NEOPLASTIC MORPHOLOGIES REMOVAL REASON: INTERCURRENT	SEX: FEMALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	20	29	26	24	27
BONE MARROW						
EXAMINED		19	29	26	24	27
MISSING		1	0	0	0	0
Histiocytic sarcoma..(MALIGNANT)		0	0	0	1	0
CERVIX						
EXAMINED		18	27	25	22	25
MISSING		2	2	1	2	2
Histiocytic sarcoma..(MALIGNANT)		1	2	1	2	1
GENERALISED NEOPLASIA						
EXAMINED		8	16	13	10	15
Composite lymphoma..(MALIGNANT)		5 62%	10 62%	11 85%	6 60%	15 100%
Lymphoblastic/lymphocytic lymphoma..(MALIGNANT)		0	0	1	2	0
Histiocytic sarcoma..(MALIGNANT)		1	5	1	2	0
Myeloid leukaemia..(MALIGNANT)		1	1	0	0	0
Lymphoma..(MALIGNANT)		1	0	0	0	0
HARDERIAN GLAND						
EXAMINED		18	28	26	23	27
MISSING		2	1	0	1	0
Adenoma..(BENIGN)		0	0	1	0	0
JEJUNUM						
EXAMINED		19	25	24	22	26
MISSING		1	4	2	2	1
Histiocytic sarcoma..(MALIGNANT)		0	0	0	0	1
KIDNEY						
EXAMINED		20	29	26	24	27
Sarcoma..(MALIGNANT)		0	0	1	0	0
LIVER						
EXAMINED		20	29	26	24	27

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TABLE 18
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)

NEOPLASTIC MORPHOLOGIES REMOVAL REASON: INTERCURRENT	SEX: FEMALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	20	29	26	24	27
LIVER (CONTINUED)						
Angiosarcoma..(MALIGNANT)		1	1	0	2	1
Histiocytic sarcoma..(MALIGNANT)		3	3	2	4	6
Composite lymphoma..(MALIGNANT)		1	0	1	0	0
LUNG						
EXAMINED		20	29	26	24	27
Adenoma..(BENIGN)		0	1	1	1	0
Adenocarcinoma..(MALIGNANT)		1	0	0	0	0
LYMPH NODE-HEPATIC						
EXAMINED		7	6	7	6	3
Composite lymphoma..(MALIGNANT)		0	0	0	1	0
LYMPH NODE-MESENTERIC						
EXAMINED		20	29	25	22	27
MISSING		0	0	1	2	0
Composite lymphoma..(MALIGNANT)		2	1	0	0	0
Histiocytic sarcoma..(MALIGNANT)		0	1	1	1	0
Lymphoblastic/lymphocytic lymphoma..(MALIGNANT)		0	1	0	0	0
OVARY						
EXAMINED		20	29	26	23	25
MISSING		0	0	0	1	2
Adenoma..(BENIGN)		0	0	1	1	0
Histiocytic sarcoma..(MALIGNANT)		0	0	0	1	0
PITUITARY GLAND						
EXAMINED		18	27	18	20	21
MISSING		2	2	8	4	6
Adenoma..(BENIGN)		3	3	3	2	3
Carcinoma..(MALIGNANT)		0	0	0	0	1
SPLEEN						
EXAMINED		20	29	26	24	27

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TABLE 18
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NEOPLASTIC MORPHOLOGIES REMOVAL REASON: INTERCURRENT	SEX: FEMALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	20	29	26	24	27
SPLEEN (CONTINUED)						
Composite lymphoma..(MALIGNANT)		0	0	1	0	0
Angiosarcoma..(MALIGNANT)		0	0	1	0	0
Histiocytic sarcoma..(MALIGNANT)		0	0	0	0	1
SUBCUTANEOUS TISSUE						
EXAMINED		2	6	2	0	3
Fibrosarcoma..(MALIGNANT)		0	0	1	0	0
Histiocytic sarcoma..(MALIGNANT)		0	1	0	0	0
UTERUS						
EXAMINED		20	29	26	24	27
Adenoma..(BENIGN)		0	0	0	1	0
Adenocarcinoma..(MALIGNANT)		1	0	0	0	0
Histiocytic sarcoma..(MALIGNANT)		1	2	1	2	1
Leiomyoma..(BENIGN)		0	0	0	1	1

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INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)

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NEOPLASTIC MORPHOLOGIES REMOVAL REASON: TERMINAL	SEX: MALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	MALES ON STUDY ANIMALS COMPLETED	50 25	50 28	50 28	50 31	50 25
ADRENAL GLAND						
EXAMINED		24	28	28	30	23
MISSING		1	0	0	1	2
Cortical adenoma..(BENIGN)		1	0	0	0	0
BLADDER						
EXAMINED		24	27	28	31	24
MISSING		1	1	0	0	1
Histiocytic sarcoma..(MALIGNANT)		0	1	0	0	0
EPIDIDYMIS						
EXAMINED		25	28	28	31	25
Histiocytic sarcoma..(MALIGNANT)		2	1	0	0	0
GENERALISED NEOPLASIA						
EXAMINED		19	14	13	19	16
Composite lymphoma..(MALIGNANT)		19	14	13	19	16
HARDERIAN GLAND						
EXAMINED		25	27	28	31	25
MISSING		0	1	0	0	0
Cystadenoma..(BENIGN)		0	1	0	0	0
LIVER						
EXAMINED		25	28	28	31	25
Hepatocellular adenoma..(BENIGN)		1	0	1	1	2
Hepatocellular carcinoma..(MALIGNANT)		0	0	0	1	0
Angiosarcoma..(MALIGNANT)		1	2	2	3	1
Histiocytic sarcoma..(MALIGNANT)		0	0	0	0	1
LUNG						
EXAMINED		25	28	28	31	25

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TABLE 18
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)

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NEOPLASTIC MORPHOLOGIES REMOVAL REASON: TERMINAL	SEX: MALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	MALES ON STUDY ANIMALS COMPLETED	50 25	50 28	50 28	50 31	50 25
LUNG	(CONTINUED)					
Adenoma..(BENIGN)		1	0	3	1	2
Adenocarcinoma..(MALIGNANT)		0	1	0	1	0
LYMPH NODE-INGUINAL						
EXAMINED		0	0	0	1	0
Angiosarcoma..(MALIGNANT)		0	0	0	1	0
LYMPH NODE-MESENTERIC						
EXAMINED		25	28	28	31	25
Composite lymphoma..(MALIGNANT)		1	0	1	1	0
LYMPH NODE-THYMIC						
EXAMINED		6	6	7	9	6
Composite lymphoma..(MALIGNANT)		0	0	0	1	0
Histiocytic sarcoma..(MALIGNANT)		0	1	0	0	0
PITUITARY GLAND						
EXAMINED		23	24	25	30	21
MISSING		2	4	3	1	4
Adenoma..(BENIGN)		1	0	0	1	0
PREPUTIAL GLAND						
EXAMINED		24	26	28	31	24
MISSING		1	2	0	0	1
Histiocytic sarcoma..(MALIGNANT)		1	0	1	0	0
SKIN						
EXAMINED		25	28	28	31	25
Rhabdomyosarcoma..(MALIGNANT)		1	0	0	0	0
SPLEEN						
EXAMINED		25	28	28	31	25

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TABLE 18
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NEOPLASTIC MORPHOLOGIES REMOVAL REASON: TERMINAL	SEX: MALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	MALES ON STUDY ANIMALS COMPLETED	50 25	50 28	50 28	50 31	50 25
SPLEEN (CONTINUED)						
Angiosarcoma..(MALIGNANT)		0	0	1	0	0
STOMACH						
EXAMINED		25	28	28	30	25
MISSING		0	0	0	1	0
Squamous papilloma..(BENIGN)		0	0	0	2	0
Papilloma..(BENIGN)		0	0	0	1	0
SUBCUTANEOUS TISSUE						
EXAMINED		1	0	1	0	0
Fibroma..(BENIGN)		0	0	1	0	0
Neurofibrosarcoma..(MALIGNANT)		1	0	0	0	0
TESTIS						
EXAMINED		25	28	28	31	25
Histiocytic sarcoma..(MALIGNANT)		1	1	1	1	1
THYMUS						
EXAMINED		20	26	25	23	21
MISSING		5	2	3	8	4
Composite lymphoma..(MALIGNANT)		0	0	1	1	0
THYROID GLAND						
EXAMINED		23	28	27	31	23
MISSING		2	0	1	0	2
Adenoma..(BENIGN)		0	1	1	0	1

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TABLE 18
INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)

NEOPLASTIC MORPHOLOGIES REMOVAL REASON: TERMINAL	SEX: FEMALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY ANIMALS COMPLETED	50 30	50 21	50 24	50 26	50 23
ADRENAL GLAND						
EXAMINED		29	21	23	26	23
MISSING		1	0	1	0	0
Cortical adenoma..(BENIGN)		1	0	0	0	0
BLADDER						
EXAMINED		30	21	23	23	23
MISSING		0	0	1	3	0
Histiocytic sarcoma..(MALIGNANT)		1	0	0	0	0
BONE MARROW						
EXAMINED		30	21	24	26	23
Angioma..(BENIGN)		0	0	1	0	0
BONE(FEMUR)						
EXAMINED		30	21	24	26	23
Osteosarcoma..(MALIGNANT)		0	0	1	0	0
CERVIX						
EXAMINED		28	19	24	25	21
MISSING		2	2	0	1	2
Histiocytic sarcoma..(MALIGNANT)		2	0	1	1	1
GENERALISED NEOPLASIA						
EXAMINED		24	15	14	9	21
Composite lymphoma..(MALIGNANT)		24	15	14	8	18
Histiocytic sarcoma..(MALIGNANT)		1	0	1	1	4
HARDERIAN GLAND						
EXAMINED		29	21	23	26	23
MISSING		1	0	1	0	0
Adenoma..(BENIGN)		1	0	0	0	0
LIVER						
EXAMINED		30	21	24	26	23

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INTERGROUP COMPARISON OF NEOPLASTIC FINDINGS (INTERCURRENT/TERMINAL)

NEOPLASTIC MORPHOLOGIES REMOVAL REASON: TERMINAL	SEX: FEMALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	30	21	24	26	23
LIVER (CONTINUED)						
Hepatocellular adenoma..(BENIGN)		0	1	0	0	0
Angiosarcoma..(MALIGNANT)		2	0	0	0	0
Histiocytic sarcoma..(MALIGNANT)		1	0	0	0	0
LUNG						
EXAMINED		30	21	24	26	23
Adenoma..(BENIGN)		1	1	0	0	1
Adenocarcinoma..(MALIGNANT)		0	0	1	0	0
LYMPH NODE-HEPATIC						
EXAMINED		3	1	0	4	6
Composite lymphoma..(MALIGNANT)		0	1	0	1	0
Histiocytic sarcoma..(MALIGNANT)		0	0	0	1	0
LYMPH NODE-MESENTERIC						
EXAMINED		30	21	24	26	23
Composite lymphoma..(MALIGNANT)		0	0	2	0	0
LYMPH NODE-THYMIC						
EXAMINED		5	9	6	5	8
MISSING		0	1	0	0	0
Histiocytic sarcoma..(MALIGNANT)		0	1	0	0	0
OVARY						
EXAMINED		29	21	23	26	21
MISSING		1	0	1	0	2
Granulosa cell tumour..(BENIGN)		0	0	0	1	0
Haemangioma..(BENIGN)		0	1	0	0	0
PITUITARY GLAND						
EXAMINED		28	19	23	25	21
MISSING		2	2	1	1	2

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NEOPLASTIC MORPHOLOGIES REMOVAL REASON: TERMINAL	SEX: FEMALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	30	21	24	26	23
PITUITARY GLAND	(CONTINUED)					
Adenoma..(BENIGN)		6	8	8	8	3
SKIN						
EXAMINED		30	21	24	26	23
Fibroma..(BENIGN)		0	1	0	0	0
SKULL						
EXAMINED		0	0	0	0	1
Osteosarcoma..(MALIGNANT)		0	0	0	0	1
SUBCUTANEOUS TISSUE						
EXAMINED		1	0	1	0	0
Histiocytic sarcoma..(MALIGNANT)		0	0	1	0	0
THYMUS						
EXAMINED		28	20	23	24	20
MISSING		2	1	1	2	3
Histiocytic sarcoma..(MALIGNANT)		0	1	0	0	0
THYROID GLAND						
EXAMINED		30	21	24	26	21
MISSING		0	0	0	0	2
Adenoma..(BENIGN)		1	0	1	0	0
Parafollicular cell tumour..(BENIGN)		0	1	0	0	0
UTERUS						
EXAMINED		30	20	23	26	23
MISSING		0	1	1	0	0
Adenoma..(BENIGN)		1	0	0	0	0
Adenocarcinoma..(MALIGNANT)		0	0	0	0	1
Histiocytic sarcoma..(MALIGNANT)		0	1	2	2	1

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NEOPLASTIC MORPHOLOGIES REMOVAL REASON: TERMINAL	SEX: FEMALES	Dietary concentration of Flutriafol 0 ppm	0 ppm	10 ppm	50 ppm	200 ppm
	FEMALES ON STUDY	50	50	50	50	50
	ANIMALS COMPLETED	30	21	24	26	23
UTERUS	(CONTINUED)					
Angioma..(BENIGN)		0	0	1	0	0
Composite lymphoma..(MALIGNANT)		0	0	0	1	0